

Human Vaccines & Immunotherapeutics: News

Agenus brain cancer vaccine improves survival in phase 2 trial

The biotech company Agenus recently reported positive results from an analysis of a phase 2 trial in patients with newly diagnosed glioblastoma multiforme (GBM) treated with the personalized cancer vaccines Prophage Series G-100 (HSPPC-96) in combination with the current standard of care (SOC). Treated patients showed improvement in progression-free survival (PFS) and overall survival (OS). The results support advancement to late-stage trials.

Every year, 17 000 Americans are diagnosed with GBM, a particularly aggressive form of brain cancer. This type of tumor is often resistant to standard therapies, and median survival is only ~15 mo from the time of first diagnosis.

The current phase 2 trial included 46 patients with newly diagnosed GBM treated at eight different centers across the US. Participants were treated with radiation and temozolomide as the SOC in addition to HSPPC-96 vaccination. Analyses of data collected to date show almost 18 mo median PFS, with 63% of the patients progression-free at 12 mo and 20% progression-free at

24 mo. Compared with 6.9 mo median PFS in control patients receiving SOC alone, this is a considerable improvement (160%). Median OS, the primary endpoint of the trial, is 23.3 mo and remains durable in patients treated with HSPPC-96. In this study, the 12-mo survival rate is 85% with 50% of patients still alive and being followed, with many surviving beyond the 24-mo study period. Median OS survival rate for SOC alone is 14.6 mo.

"These additional results from the Phase 2 trial of HSPPC-96 in patients with newly diagnosed GBM are extremely encouraging and certainly justify a definitive randomized study," said Dr Andrew T Parsa, Lead Clinical Investigator and Chair of Neurosurgery at Northwestern Memorial Hospital and Northwestern University Feinberg School of Medicine. "The patient-specificity and lack of toxicity, combined with patient selection to optimize immunotherapy efficacy, could position this vaccine as a break-through treatment for newly diagnosed GBM patients in the years ahead."

In addition to the phase 2 newly-diagnosed GBM trial, HSPPC-96 is being studied in a large,

randomized phase 2 trial in combination with bevacizumab (Avastin) in patients with recurrent GBM (ALLIANCE Trial). This trial is the largest brain tumor trial ever funded by the NCI and the largest vaccine trial ever conducted with Avastin (see also *HV&I* news 9–10).¹

Prophage Series (HSPPC-96) cancer vaccines are autologous therapies derived from cells extracted from the patient's tumor. As a result, Prophage Series vaccines contain a precise antigenic "fingerprint" of a patient's particular cancer and are designed to reprogram the body's immune system to target only cells bearing this fingerprint, reducing the risk of debilitating side effects often associated with chemotherapy and radiation therapy. These vaccines are being studied in two different settings of glioblastoma: newly diagnosed and recurrent disease.

Reference

1. Riedmann EM. Hum Vaccin Immunother 2013; 9:2034-7; PMID:24056006

Meningococcal meningitis cases fall 94% following vaccine introduction

As recently reported in *The Lancet*,² the serogroup A meningococcal vaccine MenAfriVac is highly effective at prevention of serogroup A invasive meningococcal (MenA) disease and carriage.

The vaccine was developed by the nonprofit organization PATH and the World Health Organization (WHO), with funding from the Gates Foundation. It was licensed in India in 2009, pre-qualified by the (WHO) in 2010 based on its safety and immunogenicity, and is being deployed across the African meningitis belt.

A team of international researchers, led by Dr Brian Greenwood from the London School of Hygiene and Tropical Medicine (UK), studied the effect of the MenA polysaccharide-tetanus toxoid conjugate vaccine on meningitis and carriage in Chad during a MenA epidemic. They obtained data for the incidence of meningitis before and after vaccination from

national records between January 2009 and June 2012. MenA carriage was studied in an age-stratified sample of residents between 1 and 29 y of a rural area roughly 13–15 and 2–4 mo before and 4–6 mo after vaccination.

Roughly 1.8 million individuals between 1 and 29 y of age had received one dose of MenAfriVac during a vaccination campaign in three regions of Chad in and around the capital N'Djamena in December 2011. The incidence of meningitis during the 2012 meningitis season in these three regions was 2.48 per 100 000, compared with 43.8 per 100 000 in regions without mass vaccination, representing a 94% decrease in meningitis cases. Interestingly, no case of MenA meningitis was reported in the three vaccinated regions, despite enhanced surveillance. Furthermore, 32 MenA carriers were identified in 4278 age-stratified individuals living in a rural area near the

capital 2–4 mo before vaccination, whereas only one MenA case was confirmed in 5001 people living in the same community 4–6 mo after vaccination. The trial was recently published in the journal *The Lancet*.²

"This is one of the most dramatic outcomes from a public health intervention that I have seen during a long career of research in Africa. There are now real prospects that the devastating effects of this infection in Africa can be prevented," said study senior author Dr Brian Greenwood.

Since 2010, 100 million people in the region have received MenAfriVac. The goal now is to continue the rollout of the vaccine to protect more of the 450 million people at risk of contracting MenA in central Africa.

While the data from Chad are very encouraging, the effectiveness and especially the duration of protection achieved with

MenAfriVac, as well as a potential shift in meningitis strain prevalence, need to be studied further.

Reference

2. Daugla D, et al. Lancet 2013; S0140-6736:61612-8; PMID:24035220

Most vaccines are safe during breastfeeding

Multiple studies over the past decade have shown that it is safe for mothers to take most vaccines and drugs while breastfeeding. Still, clear recommendations are often lacking, resulting in many mothers either stopping breastfeeding or taking medicines due to fear of adverse events.

In a clinical report recently published in the journal *Pediatrics*,³ the American Academy of Pediatrics (AAP) has summarized all the evidence on the topic to help physicians and mothers make more informed choices. The authors found that with rare exceptions, maternal immunization does not create any problems for breastfeeding infants, although questions concerning two topics often arise regarding lactation and immunization: the effect of lactation on the

infant's immune response to a vaccine, and a potential adverse effect on the infant from maternal immunization. In fact, vaccinating a breastfeeding mother against tetanus, diphtheria, whooping cough and flu can pass on the protection to the baby. Similarly, there is evidence that breastfeeding cuts the incidence of fever among vaccinated infants. While most live vaccines are not associated with virus secretion in human milk, there are two exceptions: smallpox and yellow fever vaccines. If a woman receives these vaccines while breastfeeding, the infant is at risk of developing vaccinia and encephalitis, respectively. But in all other cases, the AAP recommends that women continue breastfeeding after vaccination. The authors conclude that the benefits of breastfeeding

clearly outweigh the risk of exposure to most therapeutic agents via human milk. The clear statement about the safety of most drugs and vaccines for breastfeeding mothers will hopefully cause a shift in practitioners' advice.

"The starting point of the report, stressing that the vast majority of drugs are compatible with breastfeeding, is very important in trying to reverse the high level of anxiety and misperception of breastfeeding mothers and many health professionals," Dr Gideon Koren of The Hospital for Sick Children in Toronto told *Reuters Health*.

Reference

3. Sachs HC; Committee On Drugs. *Pediatrics* 2013; 132:e796-809; PMID:23979084; <http://dx.doi.org/10.1542/peds.2013-1985>

Promising phase 1 results for Genocea's herpes simplex virus vaccine

The US-based biotech company Genocea recently reported interim data from the first Phase 1 trial of its experimental herpes simplex virus 2 (HSV-2) vaccine, GEN-003, for the treatment of genital herpes. The vaccine appears to be well tolerated by patients, to trigger an immune response, and to slow down the rate of viral replication.

GEN-003, the first and most advanced product of Genocea, is based on the company's proprietary quick-hit vaccine production platform. This technology is special in two ways: (1) it significantly cuts down on the time it takes to discover the right antigens for a vaccine, and (2) these vaccines are designed to trigger a response from both B cells and T cells.

HSV-2 circulates in the blood, where it can be reached by B cells, but it spends most of its time hiding from those antibodies inside nerve tissue at the base of the spine, where it can grow and replicate. Immunologically trained T cells, however, have the ability to recognize this infected tissue and kill the virus. Genocea's GEN-003 is a combination of B- and T-cell antigens, adjuvanted with

Matrix-M from Isconova AB. The induced T-cell response, would hit HSV-2 while it is dormant in cells, the time between HSV-2 patients' outbreaks. Thereby the vaccine should slow down viral shedding, which occurs when HSV-2, after replicating in cells in the spinal column, migrates to the genitals.

To test this theory, 143 volunteers with a history of moderate-to-severe recurrent HSV-2 infections were enrolled for the phase 1 trial. Subjects were randomized to receive low-, medium- or high-dose injections of GEN-003 (or placebo) at weeks 0, 3, and 6. From assays of samples that patients collected, the rate of viral shedding was reduced by up to 51% in the high-dose group compared with placebo, and that number correlated with increased T- and B-cell responses.

"To be clear, you don't have symptoms unless you have viral shedding. We powered the study for viral shedding because there are way more [of these] events, than outbreak events," explained Dr Chip Clark, CEO of Genocea.

Genocea will track those patients over the course of a year for durability of the subjects' responses, and whether its scientific

hypothesis translates to fewer outbreaks of genital blisters and sores.

While the results of the first Phase 1 trial are promising, it remains to be seen whether they translate into a clinical benefit. The big test will come next year, when the company will start a second trial that will be judged by both viral shedding rates and a reduction in disease symptoms.

The potential market for a vaccine against HSV-2 is considerable. According to Dr Clark, between the US, UK, France, Germany, Italy, Canada, and Japan, there are about 12 million HSV-2 symptomatic subjects. People with HSV-2 typically take oral antiviral drugs like valaciclovir (Valtrex) either only when they have outbreaks or daily. Genocea envisions HSV-2 subjects combining those antivirals with periodic vaccinations. Since these interventions work orthogonally, protection may be further increased.

Delayed vaccinations clearly increase risk of whooping cough

While outright refusal of all vaccines is relatively rare, more parents choose alternative immunization schedules for their children by delaying or omitting certain vaccinations in the belief that this is the safest approach. However, there is no evidence to suggest that alternative immunization schedules are safer than the ones recommended.

In contrast, a recent study in the journal *JAMA Pediatrics*⁴ shows that alternative schedules increase the likelihood of contracting disease. A team of researchers from Kaiser Permanente examined the association of undervaccination and pertussis in children 3–36 mo of age. They looked at eight managed care organizations of the Vaccine Safety Datalink between 2004 and 2010. Each laboratory-confirmed case of pertussis (72 patients) was matched to four randomly selected controls (for a total of

288 controls) by managed care organization site, sex and age at index date (the date of pertussis diagnosis for the case patient). Undervaccination for diphtheria, tetanus toxoids, and acellular pertussis (DTaP) vaccine was defined as the number of doses of DTaP vaccine that was either missing or delayed by the index date (i.e., case patients and controls could be undervaccinated by 0, 1, 2, 3, or 4 doses of DTaP vaccine, with children undervaccinated by 0 doses considered to be age-appropriately vaccinated).

Of the 72 case patients with pertussis, 12 were hospitalized and 34 (47%) were undervaccinated for DTaP by the date of pertussis diagnosis. Of the 288 matched controls, 64 (22%) were undervaccinated for DTaP vaccine. Undervaccination was strongly associated with pertussis. Children undervaccinated for 3 or 4 doses of DTaP

vaccine were about 19 and 28 times more likely, respectively, to have received a diagnosis of pertussis than children who were age-appropriately vaccinated. The study results clearly show that undervaccination with DTaP vaccine increases the risk of pertussis among children 3–36 mo of age.

“Just over a third of the cases could have been prevented had they been vaccinated on time,” lead study author Dr Jason Glanz told *Reuters*. The link between delayed vaccinations and increased risk of disease is not surprising, but the study delivers data to back the widely held suspicions. Quantifying the risk of delaying immunization against pertussis could help healthcare providers to convince skeptical parents.

Reference

4. Glanz JM, et al. *JAMA Pediatr* 2013; PMID:24019039

Positive news from early-stage HIV vaccines

Since human immunodeficiency virus (HIV) was characterized in 1983, labs worldwide have worked to develop vaccines. Many HIV vaccine failures have given developers insight into what does not work, much of which has fed back into design of new candidates, most of which are still in early stages of development.

Profectus BioSciences recently initiated a Phase 1 trial with 30 subjects to evaluate the safety and immunogenicity of a therapeutic HIV vaccine. HIV-infected adults on antiretroviral therapy (ART) receive a multi-antigen HIV plasmid DNA (Mag-pDNA: *env*, *gag*, *pol*, *nef*, *tat* and *vif*) vaccine formulated with Profectus' interleukin-12 (IL-12) adjuvant, delivered by electroporation. This is followed by a booster immunization with the Profectus recombinant vesicular stomatitis virus (rVSV)-vectored HIV vaccine delivered intramuscularly. In addition to testing safety and immunogenicity, the ability of this prime-boost regimen to address the goals of the HIV cure agenda by targeting the latent reservoir and eradicating HIV are evaluated. Preclinical studies have shown that prime-boost delivery of the HIV pDNA and HIV rVSV vaccines results in an HIV-specific cell-mediated immune (CMI) response of significantly increased magnitude and functionality compared with delivery

of HIV pDNA or HIV rVSV vaccines alone. Both vaccines were shown to be safe and immunogenic in earlier clinical studies in HIV-negative and -positive subjects.

A preventive HIV vaccine based on a genetically modified whole virus (SAV001-H) has successfully completed Phase 1. The vaccine is developed by Dr Chil-Yong Kang and his team at the Schulich School of Medicine and Dentistry with the support of Sumagen Canada. Unlike most other HIV vaccine candidates, which are based on one or few specific HIV antigens, Kang's vaccine is unique in that it uses a killed whole HIV-1, much like the killed whole virus vaccines for polio, influenza, rabies and hepatitis A. The HIV-1 is genetically engineered for safety and production in large scale. In the randomized, observer-blinded, placebo-controlled Phase 1 trial, HIV-infected adults 18–50 y of age were given vaccine or placebo intramuscularly. No serious adverse events were observed throughout the trial. In addition to safety, HIV-1 specific antibodies were monitored. Antibodies against p24 capsid antigen increased as much as 64-fold in some vaccinees, and antibodies against gp120 surface antigen increased up to 8-fold after vaccination. Antibodies against gp120 are considered to be very important, since some of them may represent the broadly

neutralizing antibodies, which seem to be the most important parameter of a protective immune response against HIV. The increased antibody titers were maintained during the 52 week trial period. SAV001-H is the first genetically modified killed whole virus vaccine (for HIV) in human clinical trial, and proving its safety was the major concern for moving on to mid-stage trials.

Last, but not least, a recent trial published in the journal *Nature* has made the HIV vaccine community sit up. Researchers from the Oregon Health and Science University in Beaverton (USA) tested a simian immunodeficiency virus (SIV) protein-expressing rhesus cytomegalovirus (RhCMV/SIV) vector in rhesus macaques. The monkeys were then challenged with SIV, a close relative of HIV. The experimental vaccine protected ~50% of monkeys,⁵ but what was more remarkable is that these monkeys slowly cleared the virus and appeared cured.⁶ Regardless of the route of challenge, RhCMV/SIV vector-elicited immune responses controlled SIVmac239 after lymphatic and hematogenous viral dissemination, and replication-competent SIV persisted in several sites for weeks to months. Over time, however, protected monkeys lost sign of SIV infection, showing a consistent lack of measurable

plasma- or tissue-associated virus, and a loss of T-cell reactivity to SIV determinants not in the vaccine. No SIV RNA or DNA sequences above background level could be detected with ultrasensitive quantitative PCR methods, just like no replication-competent SIV could be found in these animals

So far, established infections with HIV and SIV were thought to be permanent with even the most effective immune responses and

ART only able to control, but not clear, these infections. But the data from the *Nature* study provide compelling evidence for progressive clearance of the residual virus that maintains these infections, and suggest that some lentiviral reservoirs may be susceptible to the continuous effector memory T-cell-mediated immune surveillance elicited and maintained by CMV vectors. Understanding how this happened will be of central importance to

the future management of HIV-infected individuals.

Reference

5. Hansen SG, et al. *Nature* 2011; 473:523-7; PMID:21562493; <http://dx.doi.org/10.1038/nature10003>
6. Hansen SG, et al. *Nature* 2013; 502:100-4; PMID:24025770; <http://dx.doi.org/10.1038/nature12519>

Sanofi's H7N9 vaccine trial with MF59 and AS03

Clinical testing of a vaccine candidate against H7N9 avian influenza has started in the US. The vaccine developed by Sanofi Pasteur is being tested at nine sites nationwide in two Phase 2 trials sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). The potential role for adjuvants will also be examined.

"H7N9 avian influenza virus—like all novel influenza virus strains to which people have not been exposed—has the potential to cause widespread sickness and mortality," said NIAID Director Dr Anthony S Fauci. "We are now testing a vaccine candidate with and without adjuvant in an effort to prepare for and, hopefully, protect against this possibility."

The bird flu virus H7N9 emerged in China earlier this year. The virus does not cause disease in chickens, but circulates silently in poultry and reveals its presence only when passed to humans. Live poultry markets in China were pinpointed as the main threat and shut quickly, which was essential for China's success in limiting the virus' spread. H7N9 is lethal for humans, killing 44 out of 135

known cases, but fortunately the virus does not transmit easily if at all between people, which prevents it from triggering a pandemic. However, this could change when the virus picks up mutations allowing it to spread in mammals by infecting other hosts such as pigs, or mutations necessary for person-to-person transmission.

In order to prepare for this potential public health threat, the NIH is funding two clinical trials investigating a H7N9 candidate vaccine made from inactivated virus isolated in Shanghai (China) in 2013. Since H7 influenza viruses are known to elicit poor immune responses, adjuvants are being used as part of a dose-sparing strategy. The first trial will enroll up to 700 healthy adults 19–64 y of age, who will randomly receive two doses of antigen (3.75, 7.5, 15, or 45 µg) with and without Novartis' MF59 adjuvant 21 d apart. The second Phase 2 trial will enroll as many as 1000 participants, who will receive two doses (same dosages as the other trial) of the vaccine 21 d apart. In this trial, the adjuvant AS03 developed by GlaxoSmithKline will

be tested. Furthermore, two groups will receive their first vaccination with AS03 or MF59 adjuvant, then receive the alternate adjuvant at the second vaccination. MF59 is also contained in the Flud seasonal influenza vaccine licensed in Europe and Canada for use in people age ≥ 65 y. AS03 was used in a 2009 H1N1 influenza vaccine (Pandemrix) in several European countries during the 2009–2010 H1N1 influenza pandemic.

Some experts warn that the global vaccine manufacturing capacity for flu vaccines (4.5 billion doses per year), might not be sufficient in case of a pandemic. The larger dose needed for H7N9 vaccines would cut that figure even further. Even with adjuvant, it would take 17–22 weeks to grow and make a vaccine, and manufacturers would not switch from seasonal flu to pandemic vaccines until they are sure a pandemic is underway. "That means a vaccine will be too late, as it was in the last three pandemics," says Dr Michael Osterholm, from the University of Minnesota in Minneapolis.